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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/626,943	07/25/2003	Joseph T. Rubino	AM-100802	3231

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EXAMINER	
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ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/626,943	RUBINO ET AL.	
	Examiner	Art Unit	
	GREGG POLANSKY	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-21 and 31-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-21 and 31-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 11/15/2007 has been entered.

2. Applicants canceled Claim 22-30, added Claims 31-37, and presented arguments in response to the previous Office Action.

3. Claims 12-21 and 31-37 are pending and presently under consideration.

4. Applicants' amendment of the title of the invention, in response to the title objection of the previous Office Action, is acknowledged and is acceptable.

5. Applicants' arguments filed 11/15/2007 have been fully considered but they are not persuasive. Objections not reiterated from previous office actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 12-21 and 31-37 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the instant case, Claims 12, 17, 18 and 31 recite the abbreviation "CCI-779". The first use of an abbreviation in the claims should be preceded by a full recitation of the abbreviated term so it is clear exactly what the abbreviation means.

Claim Rejections - 35 USC § 103

8. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

9. Claims 12-21 remain rejected and Claims 31-37 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Azrolan et al. (U.S. Application Pub. No. 2002/0013335), in view of Waranis et al. (U.S. Patent No. 5516770) and Haeberlin et al. (UK Patent Application Publication GB 2327611).

Claim 12 is drawn to a parenteral formulation comprising rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779), an alcoholic solvent, an antioxidant, a diluent solvent, and a surfactant. Claim 13 is drawn to the parenteral formulation of Claim 12 where the alcoholic solvent is ethanol or polypropylene (elected species). Claim 14 is drawn to the parenteral formulation of Claim 12 where the antioxidant is d,l-α-tocopherol or citric acid (elected species). Claim 15 is drawn to the parenteral formulation of Claim 12 where the diluent solvent is ethanol or polyethylene glycol 400 (elected species). Claim 16 is drawn to the parenteral formulation of Claim

12 where the surfactant is polysorbate 80 (elected species). Claims 17 and 18 are drawn to the formulation of Claim 12, wherein CCI-779 comprises from about 1 mg/ml to about 25 mg/ml and from about 2.5 mg/ml to about 10 mg/ml respectively. Claim 19 is drawn to the parenteral formulation of Claim 12 wherein the antioxidant comprises from about 0.0005% to about 0.05% w/v of the formulation. Claim 20 is drawn to the parenteral formulation of Claim 12 wherein the surfactant comprises from about 0.5% to about 10% w/v of the formulation. Claim 21 is drawn to the parenteral formulation of Claim 12 wherein the solvent comprises from about 10 % to about 90% w/v of the formulation. Claim 31 is drawn to a parenteral formulation comprising about 1 mg/ml to about 25 mg/ml of CCI-779, about 10 % to about 90% w/v of an alcoholic solvent, 0.001% to about 0.5% w/v of an antioxidant, about 0.5% to about 10% w/v of a surfactant, and a diluent solvent. Claim 32 is drawn to the formulation of Claim 31, wherein the antioxidant is citric acid and the alcoholic solvent is ethanol. Claim 33 is drawn to the formulation of Claim 31, comprising ethanol, citric acid, vitamin E and propylene glycol. Claim 34 is drawn to the formulation of Claim 33, wherein the antioxidant is d,l-α-tocopherol. Claim 35 is drawn to the formulation of Claim 31, wherein the antioxidant is 0.01% w/v citric acid. Claim 36 is drawn to the formulation of Claim 31, wherein the antioxidant is a mixture of citric acid and d,l-α-tocopherol. Claim 37 is drawn to the formulation of Claim 31, wherein the surfactant is selected from the group consisting of polysorbate 20, polysorbate 80, PEG-35 castor oil, or mixtures thereof.

Azrolan et al. teach that rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) is a member of a group of compounds that are derivatives of the rapamycin nucleus. See Azrolan et al., paragraph 14. Azrolan et al. teach the parenteral administration of CCI-779 and other rapamycins and suggest a solvent of water, ethanol, glycerol, propylene glycol and polyethylene glycol or a combination thereof, a surfactant or dispersant, such as hydroxylpropylcellulose or polyethylene glycols, a preservative and an antioxidant. See Azrolan, et al., paragraphs 28 and 29 and Claim 14. Additionally, Azrolan et al. teach and incorporate by reference preferred parenteral formulations of rapamycins taught by Waranis et al. See Azrolan et al., paragraph 29.

Azrolan et al., do not teach the specific antioxidants or the specific surfactants recited in instant Claim 16. Also, Azrolan et al., do not teach the concentrations of CCI-779, antioxidant, surfactant, or solvent as specified in the claims of the instant application and recited *supra*.

Waranis et al. teach an injectable rapamycin solution comprised of a mixture of a concentrate of rapamycin in propylene glycol with a diluent of polyethylene glycol 400 and a polyoxyethylene sorbitan ester (e.g., polysorbate 80) and water (*see* Examples 1-3), yielding an injectable formulation concentration of rapamycin of 0.2 mg/ml to 4 mg/ml (*see* column 2, lines 44-47), with 0.07-9.5% polysorbate 80 and 12-87% glycols (*see* column 3, lines 29-54). These concentrations are within the concentration ranges specified in the claims of the instant application.

Waranis et al. do not teach use of an antioxidant. Waranis et al. teach formulations of rapamycins, but not CCI-779 specifically. However, Azrolan et al. teach formulations disclosed by Waranis et al. as preferred parenteral formulations for CCI-779 (*supra*).

Haeberlin et al. teach the use of various carboxylic acids to stabilize (i.e., preserve) oral and parenteral formulations of macrolides, preferably a rapamycin. The reference teaches that macrolides are unstable upon storage, undergoing a variety of different degradation reactions and an acidic environment inhibits the degradation. See page 3. The preferred acids include malonic acid, oxalic acid, citric acid, and lactic acid (*see* page 4, lines 15-22). Haeberlin et al. teach a 0.05% to 5% acid concentration range and further disclose that the preferred amount of acid may be determined by routine experimentation. Haeberlin et al. give as an example, a formulation of a rapamycin with ethanol, Cremophor® EL (a surfactant), and citric acid. They present other examples of rapamycin formulations which include the use of 1,2 propylene glycol as a solvent and d,l-α-tocopherol as an antioxidant.

With respect to claimed concentration ranges in the instant compositions, it is not inventive to discover the optimum or workable ranges by routine experimentation when general conditions of a claim are disclosed in the prior art. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233,235 (CCPA 1955) and MPEP 2144.05(11).

It would have been obvious to one of ordinary skill in the art at the time of the invention, who was motivated to produce a parenteral formulation of CCI-779, to combine the teachings of Azrolan et al., which discloses the essential elements of said

formulation, with those of Waranis et al. and Haeberlin et al., which teach individual elements of Azrolan et al. in more detail. Waranis et al. teach the concentrations of the solvents (e.g., propylene glycol and polyethylene glycol 400), rapamycin, and a specific surfactant (polysorbate 80) for a parenteral rapamycin formulation. Haeberlin et al. teach the use of citric acid and d,l-α-tocopherol as a stabilizer in a rapamycin parenteral formulation. The Azrolan et al. teaching of including an antioxidant and preservative in rapamycin formulations would have motivated one to combine Azrolan et al. with Haeberlin et al. One would have been motivated to combine Azrolan et al. and Waranis et al. since Azrolan et al. specify and incorporate by reference the parenteral formulations of Waranis et al. One would have been motivated to perfect a parental formulation of CCI-779 to reduce the bioavailability uncertainties of other forms of administration (e.g., oral), leading to more accurate and reproducible doses of the agent.

10. Applicants argue that the combination of the prior art references (*supra*) does not render the claims obvious. Applicants argue there is no prior art teaching of stability problems of parenteral formulations of CCI-779 and without recognition in the art, there would be no motivation to look for a solution. The Examiner disagrees and directs Applicants to page 3 of the Haeberlin et al. reference (also see above).

Applicants argue the teachings of Waranis et al. and Azrolan et al. do provide a parenteral formulation comprising all of the components present in the claimed invention and further, there would be no motivation to "combine what Haeberlin et al. claim is an acid-stabilized formulation with an alchoholic solvent, an antioxidant, a diluent solvent

and a surfactant. The Examiner believes the three references suggest all of the claimed formulations' components. As presented *supra* Azrolan et al. teach the parenteral formulation of CCI-779 and suggest a solvent of *inter alia*, ethanol, propylene glycol and polyethylene glycol or a combination thereof, a surfactant or dispersant, such as hydroxylpropylcellulose or polyethylene glycols, a preservative and an antioxidant, and incorporate by reference the formulations of Waranis et al. Waranis et al. teach rapamycin formulations comprised of a mixture of a concentrate of rapamycin in propylene glycol with a diluent of polyethylene glycol 400 and a polyoxyethylene sorbitan ester (e.g., polysorbate 80) and water. Haeberlin et al. teach macrolide stability issues and carboxylic acid stabilization rapamycin parenteral formulations including a formulation comprising rapamycin with ethanol, a surfactant, and citric acid.

Favorable consideration will be given to a parenteral formulation comprising ethanol and citric acid, wherein the concentration of citric acid is less than 0.01%.

Conclusion

11. Claims 12-21 and 31-37 are rejected.

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GREGG POLANSKY whose telephone number is (571)272-9070. The examiner can normally be reached on Mon-Thur 9:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregg Polansky/
Examiner, Art Unit 1611

/Phyllis G. Spivack/
Primary Examiner, Art Unit 1614